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Efficacy of Metronidazole in the Conservative Treatment for Appendiceal Mass

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Abstract

Background In patients with complicated appendicitis, interval appendectomy (IA) with a single broad-spectrum antibiotic sometimes fails. We reviewed our experience of adding metronidazole (MNZ) in such situations.

Methods Medical records of children with an appendiceal mass treated with broad-spectrum antibiotics followed by IA from March 2009 to May 2019 were reviewed. In the latter period (after April 2015, Group L, $n = 14$), MNZ was added if symptoms were not improved by a 3- to 4-day course of antibiotics. The body temperature, white blood cell count (WBC), serum C-reactive protein (CRP), treatment failure, and hospital stay for the initial treatment were collected in the earlier period (Group E, $n = 14$) and Group L.

Results There was no treatment failure. Group E tended to require a longer hospital stay (14.0 vs. 11.1 days, $p = 0.099$); however, the temperature, WBC, and CRP on admission were not significantly different. In the MNZ-added group ($n = 8$), the mean rate of change (per day) in WBC before and after the addition of MNZ were $-288 \pm 1{,}155$ and $-3{,}870 \pm 1{,}634$, respectively ($p = 0.001$). All patients underwent IA in about 3 months.

Conclusions This preliminary study may indicate the efficacy of MNZ combined with a broad-spectrum antibiotic followed by IA for intractable appendiceal masses.

Keywords
- children
- complicated appendicitis
- appendiceal mass
- interval appendectomy
- metronidazole

Introduction

Interval appendectomy (IA) has been reported to be a successful treatment for children suffering from acute perforated or mass-forming appendicitis and is associated with reduced postoperative complications, hospital stay, and cost.[1] The optimal treatment strategy for IA, especially during the initial nonoperative treatment (NOT), remains to be determined. The failure rates of NOT in the treatment of complicated appendicitis have been reported to be 10 to 48%.[1–5] The antibiotics regimen and criteria for determining failure of NOT varies in each pediatric institution.[1,6] We assumed that a more tenacious antibiotic strategy for complicated appendicitis in comparison to studies reported in the literature might improve the success rate of NOT and allow more children with complicated appendicitis to benefit from IA.

Metronidazole (MNZ) has been traditionally used in combination with ampicillin and gentamycin as part of a triple therapy to treat appendicitis[7]; however, after the emergence of recent broad-spectrum antibiotics, MNZ is usually used in second-line therapy in combination with cephem antibiotics and other agents.[8] Many studies have described the use of MNZ as postoperative treatment for appendicitis[9–12]; however, there are few reports of the administration of MNZ during initial NOT before planned IA (iNOT/pIA).[13] We herein report our preliminary study to investigate the superimposed efficacy

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of MNZ combined with a single broad-spectrum antibiotic (as iNOT/pIA) for the treatment of intractable appendiceal masses in children.

Materials and Methods

Ethical approval for this study was obtained from our Institutional Review Board (number: 2019-232). Among the 104 children who were diagnosed with acute appendicitis in our department between March 2009 and May 2019, 72 patients with complicated appendicitis without abscess were treated with emergent laparoscopic appendectomy soon after the admission, and four patients with uncomplicated appendicitis were treated conservatively without operations. INOT/pIA including broad-spectrum antibiotics was considered to be appropriate for the treatment of the remaining 28 patients who had abscess or mass-forming complicated appendicitis visualized by abdominal ultrasound or contrast-enhanced computed tomography. These patients were included in this study. From April 2015, MNZ was added if a patient did not respond well to a 3- to 4-day course of the initial treatment.

The study population with iNOT/pIA was divided into children who were treated in the earlier period (Group E; $n = 14$) from March 2009 to March 2015 and those who were treated in the latter period (Group L; $n = 14$) from April 2015 to May 2019 from which time the protocol included the additional administration of MNZ when necessary.

The demographic data of the patients, including age, gender, plasma white blood cell (WBC) count, serum C-reactive protein (CRP), body temperature on admission and during the treatment course, the intravenous antibiotics that were administered, and the period of hospital stay for the initial NOT were retrospectively collected from medical records.

Group L was divided into two subgroups; eight patients were treated with additional MNZ (Group L–M) and six were treated without MNZ (Group L-non-M) (►**Fig. 1**). The rate of change (per day) in the WBC count (ΔWBC), CRP level (ΔCRP), and temperature (ΔTemp) in the initial 3- to 4-day treatment (before the addition of MNZ in Group L–M) were compared between the two subgroups. In Group L–M, the rates of change were compared before and after the addition of MNZ.

Treatment failure was defined by a lack of clinical improvement under iNOT/pIA (persistent fever, pain, and/or bowel obstructive symptoms), irrespective of the period that was required to obtain clinical improvement.

The statistical analyses were performed using SPSS version 26 (IBM, United States). Continuous variables were reported as the mean ± standard deviation and compared by Student's *t*-test or Mann–Whitney U test if the data were or were not considered normally distributed judging from Shapiro–Wilk test, respectively. *p*-Values of <0.05 were considered to indicate statistical significance.

Results

There was no significant difference in the initial clinical data of the patients on admission between Groups E and L (►**Table 1**). Although the intravenous antibiotics that were used for the iNOT/pIA in both groups varied according to the consultants' preferences, the cefozopran or meropenem combined with clindamycin tended to be chosen as the first antibiotics in Group E, whereas piperacillin/tazobactam (PIPC/TAZ) tended to be chosen as the first antibiotics in Group L (►**Table 2**).

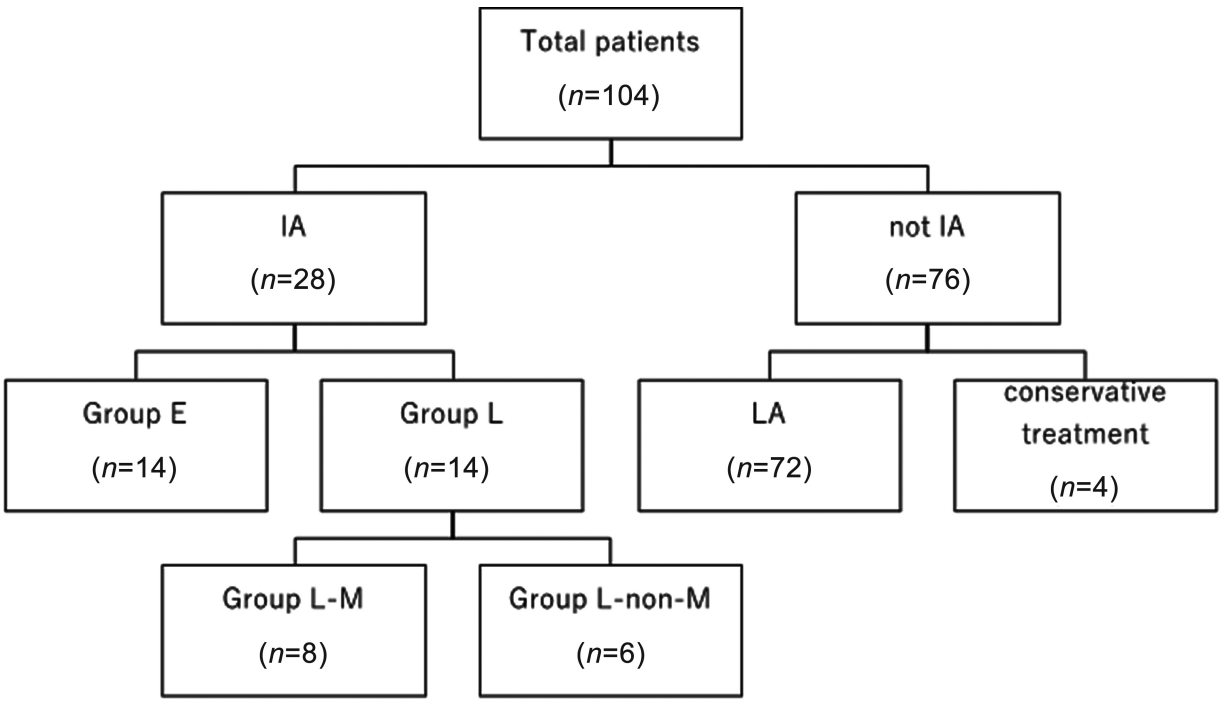

Fig. 1 The flowchart representing numbers of the patients for each treatment option. IA, interval appendectomy, LA, laparoscopic appendectomy.

Table 1 The demographic characteristics of the patients in Groups E and L, as well as the plasma white blood cell count, serum C-reactive protein, and temperature on admission

	Group E	Group L	*p*
Number of patients	14	14	–
Male:Female	8: 6	8: 6	–
Age	8.21 ± 3.45	7.43 ± 3.71	0.567
WBC on admission (/μL)	18157.1 ± 4848.6	18128.6 ± 5959.2	0.836
CRP on admission(mg/dl)	10.7 ± 5.9	13.6 ± 8.7	0.312
Temperature on admission (°C)	38.3 ± 0.8	38.2 ± 1.0	0.887
Hospital stay (d)	14.0 ± 5.5	11.1 ± 3.1	0.099

Table 2 The antibiotics used by all patients during nonoperative treatment for an appendiceal mass

Case	Group E	Case	Group L
1	ABPC/SBT, AMK, CLDM→IPM/CS, CLDM	1	CZOP, CLDM→MEPM, CLDM, MNZ
2	CZOP	2	TAZ/PIPC, MNZ
3	CEZ→CZOP	3	TAZ/PIPC→TAZ/PIPC, MNZ
4	MEMP	4	TAZ/PIPC→MEPM, MNZ
5	CZOP→CZOP, CLDM→MEPM, CLDM	5	TAZ/PIPC→TAZ/PIPC, MNZ
6	CEZ→MEPM, CLDM	6	TAZ/PIPC→TAZ/PIPC, MNZ
7	MEPM, CLDM→CZOP, CLDM	7	TAZ/PIPC→TAZ/PIPC, MNZ
8	CMZ→MEPM→MEPM, CLDM	8	CMZ→TAZ/PIPC→TAZ/PIPC, MNZ
9	MEPM, CLDM	9	MEPM, CZOP, CLDM
10	MEPN, CLDM→CZOP, CLDM→MEPN, CLDM	10	CMZ→MEPM
11	CZOP, CLDM	11	TAZ/PIPC
12	CZOP, CLDM	12	TAZ/PIPC→MEPM
13	DRPM, AMK→CZOP, AMK	13	TAZ/PIPC
14	PIPC→CTX→DRPM→CDTR-PI→CZOP	14	TAZ/PIPC

Abbreviations: ABPC/SBT, ampicillin/sulbactam; AMK, amikacin; CDTR-PI, cefditoren pivoxil; CEZ, cefazolin; CLDM, clindamycin; CMZ, cefmetazole; CTX, cefotaxime; CZOP, cefozopran; DRPM, doripenem; IPM/CS, imipenem/cilastatin; MPEM, meropenem; PIPC, piperacillin; PIPC/TAZ, piperacillin/tazobactam.
Note: Changes in the regimen are described next to the arrow '→'. ▭: Group L–M, ▭: Group L-non-M.

The serial changes of WBC, CRP, and temperature during iNOT/pIA for patients in Groups E and L are shown in ►**Figs. 2A, B–4A, B**, respectively. The comparison of those line graphs between Group E and L were impossible statistically, although there appears to be a tendency for WBC, CRP, and temperature to decrease faster in Group L than in Group E. The hospital stays for iNOT/pIA tended to be shorter in Group L than in Group E; however, these differences did not reach statistical significance (►**Table 1**).

In Group L, initial ΔWBC, ΔCRP, and ΔTemp after admission tended to be higher in Group L–M than in Group L-non-M (−288 ± 1,155 vs. −2,520 ± 2,869 [$p = 0.067$], −0.59 ± 1.07 vs. −1.92 ± 1.94 [$p = 0.172$], and −0.16 ± 0.23 vs. −0.35 ± 0.53 [$p = 0.392$], respectively). In Group L–M, the serial changes of WBC, CRP, and temperature are described with day of MNZ initiation as zero on the x-axis in ►**Fig. 5A, B, C**, respectively. The ΔWBC, ΔCRP, and ΔTemp values before and after the addition of MNZ were −288 ± 1,155 versus −3,870 ± 1,634 ($p = 0.001$), −0.59 ± 1.07 versus −1.75 ± 1.34 ($p = 0.179$), and −0.16 ± 0.23 versus −0.33 ± 0.34 ($p = 0.102$), respectively; the difference in ΔWBC was statistically significant.

As a typical example, an abscess-forming appendicitis (contrast-enhanced computed tomography) at diagnosis and its intraoperative picture at the time of the IA (3 months after the onset) with the abscess cleared in an 8-year old boy in Group L–M are shown in ►**Fig. 6A, B**, respectively.

No adverse events related to the administration of MNZ (e.g., allergic reaction, liver or kidney dysfunction, etc.) were observed in Group L–M. There was no treatment failure of iNOT/pIA in Groups E or L, although one patient in Groups E, L–M, and L-non-M was readmitted for recurrent appendicitis (all were successfully treated with antibiotics). All patients, including those who were readmitted, underwent IA approximately 3 months later without any postoperative complication. The operation time in Group L was 106.8 ± 41.1 minutes, which was significantly longer than 75.5 ± 17.7 minutes in Group E

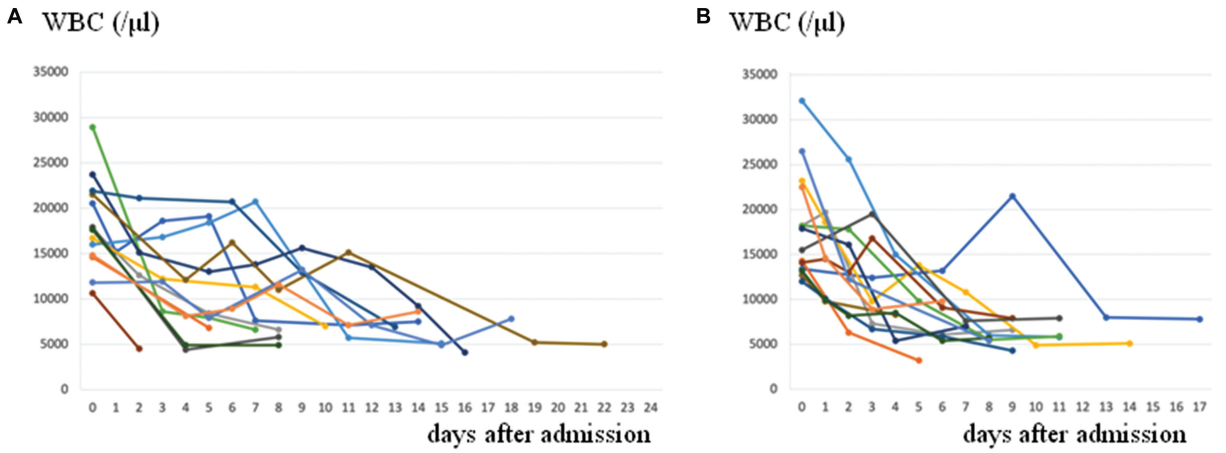

Fig. 2 Serial changes in the plasma white blood cell (WBC) count in Groups E (A) and L (B).

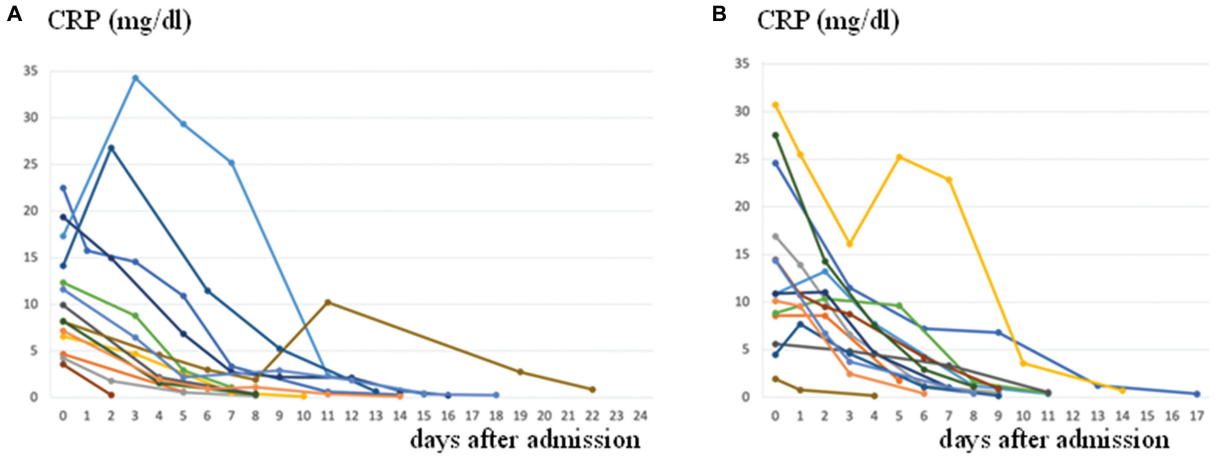

Fig. 3 The serial changes in serum C-reactive protein (CRP) in Groups E (A) and L (B).

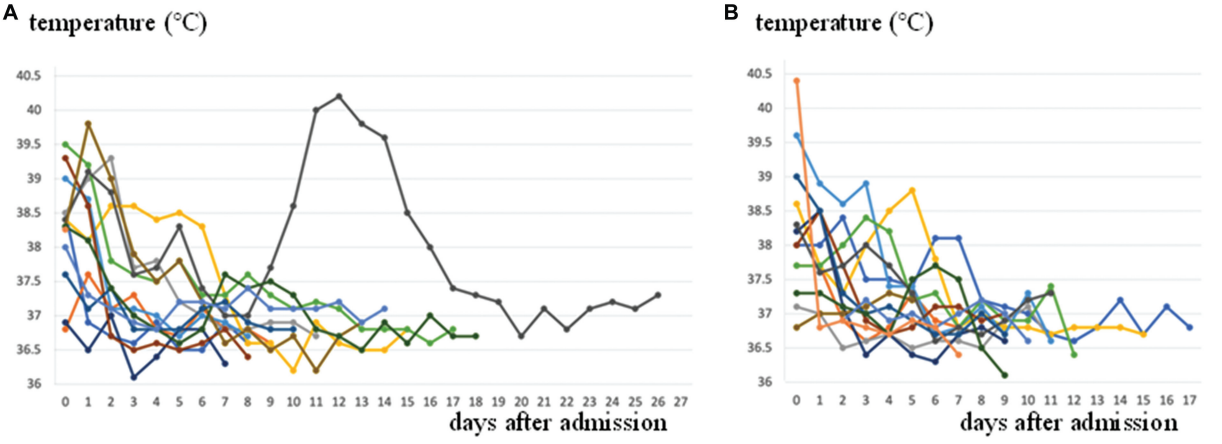

Fig. 4 The serial changes in temperature in Groups E (A) and L (B).

($p = 0.018$), but those difference did not reach statistical significance between 116.4 ± 41.1 minutes in Group L–M and 94.0 ± 41.1 minutes in Group L-non-M ($p = 0.333$).

Discussion

Acute appendicitis remains the most common indication of emergent abdominal surgery in children. Advanced appendicitis with perforation may occur in 30 to 60% of pediatric cases, especially in younger children,[14] which is partly explained by a delay in the diagnosis due to frequent nonspecific symptoms. Various clinical prediction rules have been introduced trying to standardize the diagnostic approach to appendicitis,[15] some of which are specifically applied to children, such as Pediatric Appendicitis Score[16] and Pediatric Appendicitis Risk Calculator.[17] The accuracy of

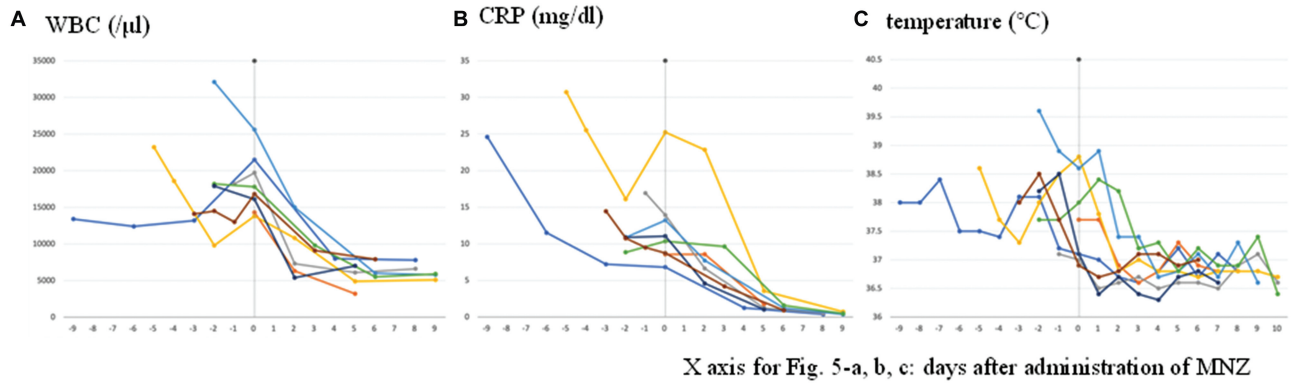

Fig. 5 The serial changes in the white blood cell (WBC) count (**A**), C-reactive protein (CRP) level (**B**), and temperature (**C**) in Group L–M. The day on which MNZ was initiated is day zero on the x-axis.

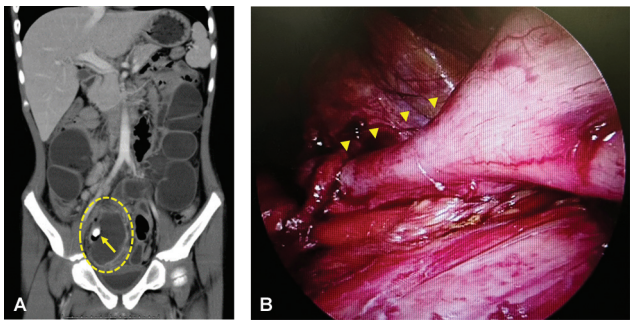

Fig. 6 (**A**) A coronal view of the contrast-enhanced computed tomography at diagnosis of an 8-year-old boy in Group L–M, showing a swollen appendix with an appendicolith (arrow), accompanied by an adjacent abscess (dotted circle). (**B**) The intraoperative picture of the same patient at the time of the interval appendectomy in 3 months after the onset, showing no abscess and little adhesion around the appendix (arrowheads).

these scoring systems in diagnosing acute appendicitis seems inconsistent, possibly due to variation in interrater reliability of clinical findings for those scores.[17] Furthermore, although classic presentation of appendicitis may often be noted in school-age children and adolescents, making correct diagnosis of acute appendicitis is challenging in younger children because of frequent absence of classical clinical features.[18] The surgical treatment with laparoscopic appendectomy for acute appendicitis in children is a golden standard.[19] The management of complicated appendicitis, especially with inflammatory appendiceal mass, however, is controversial[20]; immediate appendectomy in those situations may be hazardous and technically demanding because of the distorted anatomy and the difficulties to close the appendiceal stump because of the inflamed tissues,[21] and it has been shown to be associated with more complications, more reoperations, and longer hospital stay.[2,22]

Initial NOT followed by planned interval appendectomy (iNOT/pIA) in approximately 12 weeks has been one of the recommended strategies for patients with localized inflammatory mass.[23,24] Although initial NOT for complicated appendicitis is successful in most cases, those failure rates are reported to range between 10 and 41%, associated with increased complication rates, and longer length of hospital stay.[6] We then considered that modifying the initial antibiotic therapy during iNOT/pIA for intractable complicated appendicitis may decrease the failure rate of NOT, leading to more successful delayed appendectomies. Broad-spectrum, single-, or double-agent therapy is considered to be as effective as and more cost-effective than triple-agent therapy for the treatment of perforated appendicitis,[25] and piperacillin–tazobactam or meropenem as a single broad-spectrum antibiotic, and ceftriaxone and MNZ as double agents have been typically used in those situations.[6,9]

Shang et al[11] reported no benefits of adding MNZ to single broad-spectrum antibiotics in treating perforated appendicitis postoperatively in children. However, no study has ever been conducted to analyze the efficacy of MNZ in the setting of iNOT/pIA for complicated appendicitis in children. To the best of our knowledge, this is the first report to indicate the possible superimposed efficacy of MNZ added to broad-spectrum antibiotics as a rescue therapy during iNOT/pIA for intractable complicated appendicitis in children. The sharp decline in ΔWBC after the addition of MNZ in Group L–M was prominent and a similar tendency was observed in ΔCRP and ΔTemp (►**Fig. 5A–C**). Our rough comparisons of the serial changes of WBC, CRP, and temperature between Groups E and L (not based on statistical analysis) appear to indicate that the control of iNOT/pIA was better in Group L (in which MNZ was added when needed) than in Group E, in which the addition of MNZ was not an option. This may also explain why the hospital stay of Group L was 3 days shorter than that of Group E. We reviewed the clinical data of the patients in Group E, and in 7 (case numbers 1, 5, 7, 10, 11, 13, 14) of the 14 cases (50%) the addition of MNZ would have been appropriate because the patients showed inadequate clinical improvement during iNOT/pIA; thus, it might have been possible for the patients to return home earlier.

The operation time in Group L was significantly longer than that in Group E ($p = 0.018$). The operation time in IA may be partly influenced by the adhesion around the appendixes and/or skillfulness of the operators, but those data could not be analyzed in this study. Considering that those difference did not reach statistical significance between in Group L–M and in Group L-non-M ($p = 0.333$), usage of MNZ did not seem to negatively impact on the surgical outcome of iNOT/pIA in this study.

The protocol of the antibiotics regimen and the criteria determining failure of NOT vary in each pediatric institution. Talishinskiy et al[6] reported that they started NOT for children with perforated appendicitis with broad-spectrum intravenous antibiotics (PIPC/TAZ or meropenem) until they became afebrile, pain free, and could tolerate a regular diet. Oral antibiotics were continued for an additional week after discharge, followed by IA after an 8-week interval. They defined treatment failure based on the absence of a clinical improvement in the abovementioned symptoms during NOT or the need for readmission for additional intravenous antibiotics and/or early appendectomy. Kogut et al[1] treated pediatric patients with perforated appendicitis with intravenous antibiotics (ceftazidime and clindamycin) until they became afebrile for 48 consecutive hours and their WBC counts and differential counts normalized, and then performed IA 8 to 12 weeks later. They defined treatment failure as a lack of improvement in the clinical condition within 72 hours of the start of antibiotics or the performance of early appendectomy. If the criteria for failure in NOT reported by Kogut et al[1] were applied to our patients in Groups E and L, treatment failure would have occurred and early appendectomy would have been indicated in 15 out of the 28 (54%) cases. Our regimen of adding MNZ as a rescue therapy may reduce the failure rate of iNOT/pIA and allow more children with complicated appendicitis to benefit from IA, although their hospital stay may become longer.

The combination of recent broad-spectrum antibiotics and MNZ has been discouraged because of overlapping anaerobic coverage.[11,26] However, the fact that the addition of MNZ to PIPC/TAZ seemed to enhance the effectiveness of iNOT/pIA in Group L–M may indicate that some anaerobes that are less sensitive to PIPC/TAZ and more sensitive to MNZ might have contributed to sequelae. The patients in our study did not undergo abscess drainage during iNOT/pIA. The assessment of the bacterial profile and antimicrobial sensitivity pattern of bacterial isolates from abscesses or the appendiceal cavity would help to establish an appropriate antibiotic protocol for iNOT/pIA for the treatment of complicated appendicitis.

The present study was associated with several important limitations. It was a single-center case-series study with a relatively small number of patients. The antibiotic regimens displayed a relatively high degree of variation, especially in Group E, and the timing at which the clinical data were collected varied. Our data lacked information from imaging studies to support the estimation of the severity of appendicitis on admission.

In conclusion, this preliminary study may indicate the superimposed efficacy of MNZ combined with a broad-spectrum antibiotic followed by IA in the treatment of intractable appendiceal masses. More studies are needed to clarify the bacterial profile causing intractable appendicitis and possible indications of overlapping antibiotics coverage in that setting.

Authors' Contribution
H.S. and M.Y. designed the study. S.O., K.Ma., K.K., K.Mi., Y.M., and Y.G. manage the patients. S.O. collected the data, and S.O., H.S., and H.T. analyzed the data. S.O. wrote the draft and H.T. critically reviewed the manuscript.

Conflict of Interest
None declared.

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